Reaction of Alkylhydrazines. 3. Reaction of Methylhydrazine and 1,1-Dimethylhydrazine with *cis*- and *trans*-Cyclohexane-1,2-dicarboxylic Anhydrides. Products and Reaction Sequence[1,2]

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The reaction of methylhydrazine (**1**) and 1,1-dimethylhydrazine (**2**) with the *cis*- and *trans*-cyclohexanedicarboxylic anhydrides (**3** and **4**, respectively) under controlled conditions has provided a series of hydrazine-containing compounds with potential significance for medicinal chemistry.[3] The single crystal x-ray and spectral analyses of the products enabled us to elucidate the pathways involved in these reactions. A possible applicability of the chemistry of the reactions to analogous systems is envisaged.

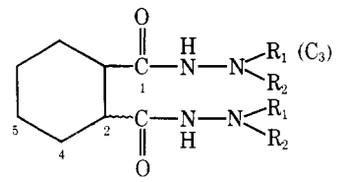
Results and Discussion

At room temperature the reaction of equimolar quantities of **1** and **3** afforded a 70:30 mixture of *cis*-*N*-methylaminocyclohexane-1,2-dicarboximide (**6**) and *cis*-2-methylcyclohexa[*d*]pyridazine-1,4-dione (**8**) (Scheme I). These products were separated by differential solubility and their structures were determined by ir, NMR, and MS spectrometries and microanalyses (data in Table II). The configuration of **6** was determined by a single crystal x-ray analysis[4] and **8** by a spectral comparison with its isomer, **9**, established by x-ray analysis to be trans.[4]

Heating **3** with excess **1** gave as an end product cyclohexane-1,2-bis(2-methylcarbohydrazide) (**10**) which proved to be trans by comparison of its ^{13}C NMR spectrum (Table I) with that of the tetramethyl analogue, **20**, a trans configuration according to the x-ray analysis.[5] The sequence of the reaction of **3** with **1** was determined by carefully monitoring the formation of the reaction intermediates at 5-min intervals by using thin layer chromatography, followed by a workup on the samples of interest. The structure elucidation was carried out by comparison of the spectra of each compound with those prepared under predetermined conditions and structurally established.

The first compound in the reaction sequence was assumed to be the methylhydrazinium salt or half acid-hydrazide (**5**), similar to its structurally identified analogues **17b** (vide infra). A rapid rate of cyclization of **5** to **6** did not permit its isolation. Treatment of **6** with **1** gave **7**, detected by TLC as a very unstable species in the hot reaction medium, but stable enough for isolation from the reaction at room temperature. The structure and configuration of **7** were proven by elemental analysis and comparison of its spectral data with those of **10**.

Table I. ^{13}C Chemical Shifts,[a] ppm



$R_1 = CH_3$; $R_2 = H$ (**10**)

$R_1 = R_2 = CH_3$ (**14**, **20**)

Compd	C_1	C_2	C_3	C_4	C_5
10	175.812	45.356	38.202	29.357	25.065
14	174.382	46.786	42.429	26.691	23.179
20	174.899	46.979	45.548	29.550	25.258

[a] Chemical shift reference, Me_4Si; solvent, D_2O.

Scheme I

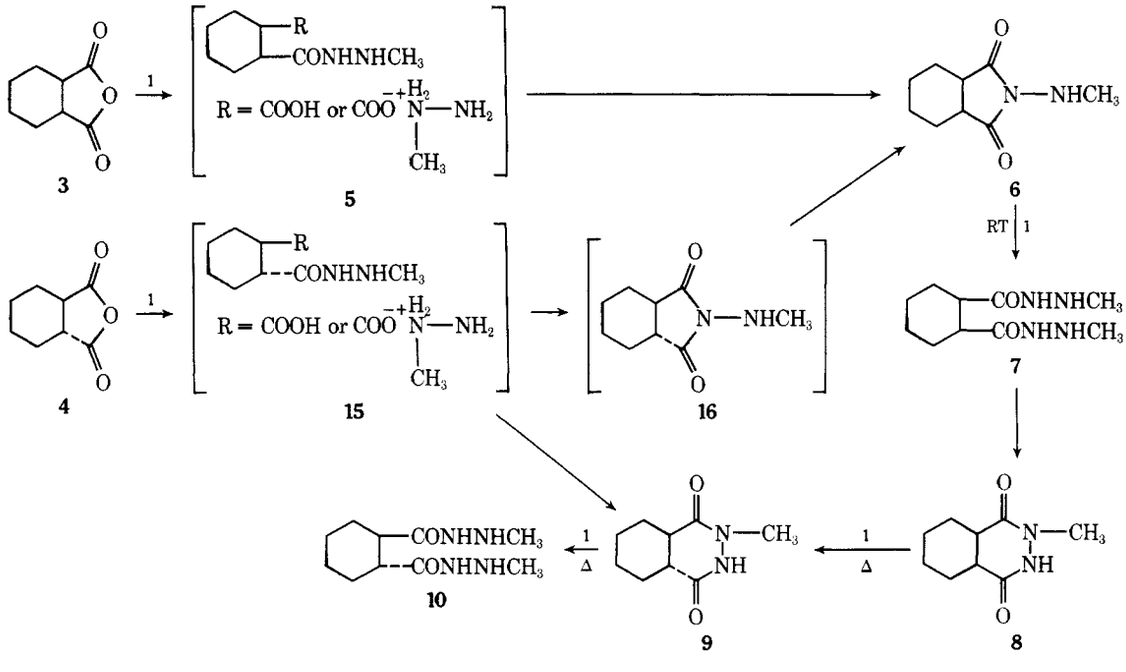


Table II.[a] Physical Properties of the Products

Compd	Yield,[b] %	Crystn solvent	Mp, °C	Ir (KBr), cm^{-1} C=O	Ir (KBr), cm^{-1} NH	NMR, δ, ppm (TFA–TPP) CH_3	NMR, δ, ppm (TFA–TPP) C_6H_{10}
6	60[c] 20[d]	C_7H_{16}–CH_3OH	94–95	1690 1770	3270	3.30 (s)	1.35–3.45 (m)
7[e]	50		116–120	1635	3250	3.18 (s)	1.33–3.23 (m)
8	20[c] 10[d]	C_6H_6–CH_3OH	171–172	1650	3200	3.40 (s)	1.30–3.25 (m)
9	64	C_6H_6–CH_3OH	226–227	1660	3200	3.35 (s)	1.00–2.70 (m)
10	81[c] 87[d]	C_6H_6–CH_3OH	239–240	1640	3280	3.25 (s)	1.15–3.05 (m)
12[g]	77		185–187	1545 1650		3.40 (s) 2.93[f] (t)	1.30–2.67 (m)
13	95[c] 30[d]	C_7H_{16}	69–70	1720 1770		3.63 (s)	1.30–3.35 (m)
14	80	C_6H_6–CH_3OH	194–195	1655	3210	3.40 (s)	1.40–3.15 (m)
17a	75	C_6H_6–CH_3OH	118–120	1710 1650	3250	3.40 (s)	1.20–3.0 (m)
17b[g]	97		121–124	1540 1640	3200	3.40 (s) 3.23 (s)	1.10–3.10 (m)
19	8	C_7H_{16}–$CH_3COOC_2H_5$	137–138	1660		3.65 (s)	1.20–3.50 (m)
20	40	C_6H_6–CH_3OH	258–260	1670	3220	3.28 (s)	1.10–2.95 (m)

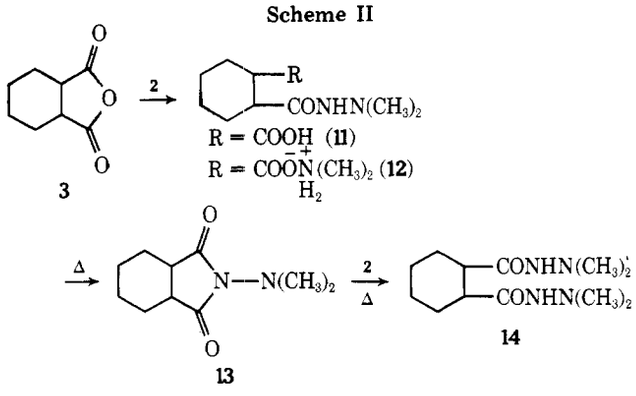
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all the compounds in this table. Compounds 12 and 17b were not analyzed. [b] Partially purified product with melting point lower than that of the analytical samples. [c] Percent yield from the cis anhydride, 3. [d] Percent yield from the trans anhydride, 4. [e] Due to the lack of stability, 7 could not be crystallized. The sample for analysis was washed with dry ether. [f] The triplet in the NMR spectrum of 12 results from $H_2N^+(CH_3)_2$. The dimethylhydrazinium salt $H_2NN^+H(CH_3)_2$ moiety of 17b gives only a singlet at δ 3.23. [g] The organic salts 12 and 17b were not amenable to crystallization. The lack of broad melting range after washing with ether was indicative of the reasonable purity of the compounds.

In solution at room temperature 7 was slowly transformed to 8. This rate was increased significantly at the elevated temperature.

The rapid rate of formation of 6 in the course of the reaction of 3 with 1 (TLC detected), as well as transformation of a pure sample of 6 to 8 (via 7) in the presence of 1, seemed to indicate the lack of direct formation of 8 from 5. In contrast, the equimolar reaction of the trans anhydride, 4, with 1 (Scheme I) provided a 25:10:60 mixture of 6, 8, and 9 with 9 resulting directly from 15. Apparently the reaction intermediate, 15, may cyclize both by the reaction of N_2 and N_1 of the hydrazide moiety with carboxylic C=O to give respectively a relatively stable *trans*-cyclohexapyridazine (9) and a relatively unstable trans imide, 16, which isomerized to 6, the precursor of 8. Upon heating with 1, 8 was isomerized to 9 which was then converted to 10. The failure of 8 to isomerize to 9 in the presence of triethylamine, pyridine, or piperidine indicated that a base with the strength of 1 is apparently necessary for pulling off the methine proton from 8 to effect isomerization.

The course of the reaction of 3 with 2 (Scheme II) differed

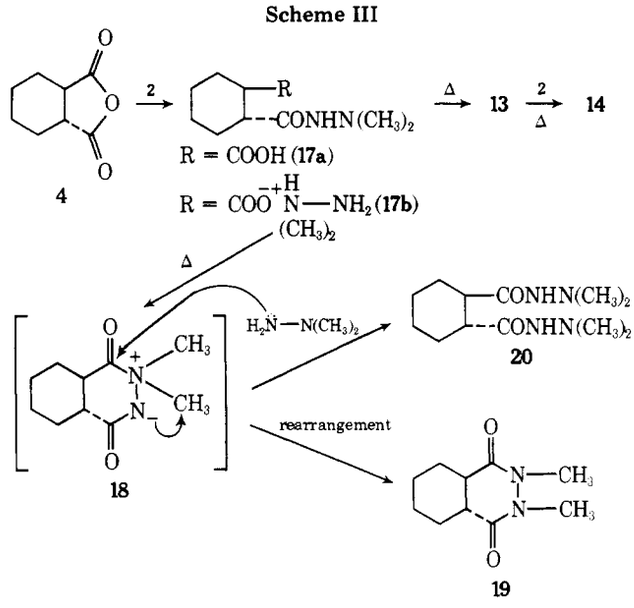
Scheme II



in two ways from that of 3 with 1. First, the dimethylammonium salt[6] (12) of the half acid-hydrazide (11), unlike that of 5, was amenable to purification and upon heating gave 13. Second, heating 13 with 2 gave only a cis dihydrazide, 14. This was probably due to the resistance of 14 to undergo cyclization like 7 to 8, the precursors of 10. The configuration of the imide, 13, was assumed to be cis analogous to that of 6, the only imide obtained from the reaction of both cis and trans anhydrides with 1.

When the anhydride 4 was treated with 2 (Scheme III), both

Scheme III



the half acid-hydrazide (17a) and its dimethylhydrazinium salt[5] (17b) were isolated and characterized (Table II). Heating 17a or 17b with 2 gave a mixture of 13, 19, and 20 in the ratio of 30:10:50.

Similar to the reaction of 4 with 1, 17a in part cyclizes to the unstable trans imide whose isomerization affords 13, the precursor of 14. Cyclization of 17a by the attack of N_2 of the hydrazide on C=O gives the inner salt, 18. Rearrangement of 18 gives 19 or its reaction with 2 gives 20.

Elucidation of the pathways in the reactions of the cyclohexane-1,2-dicarboxylic anhydrides with methylhydrazine and 1,1-dimethylhydrazine seems to possess general applicability. The scope and limitation of the hydrazine–anhydride reactions are being investigated in our laboratory.

Experimental Section

Melting points, uncorrected, were determined on a Thomas-Hoover apparatus using open capillaries. Infrared spectra were recorded on a Beckman IR-8, using KBr disks for the solid compounds and smears on sodium chloride for the semisolid and liquid compounds. Only the bands for C=O and NH stretching frequencies in wavenumber ν_{max} (cm^{-1}) were reported. ^1H NMR spectra were determined on a JEOL C-60 HL and R-12 using trifluoroacetic acid (TFA) as a solvent and sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TTP) as a reference. ^{13}C NMR spectra were determined on a Bruker WH-90 using D_2O as a solvent and Me_4Si as reference. The mass spectra were measured on a Du Pont 21-491 instrument. The thin layer chromatography was done on microscope slides coated with silica gel HF 254 + 366 (Brinkmann Instruments, Inc.). All evaporations were carried out in vacuo in a rotatory evaporator. The elemental analyses were done by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. The single crystal x-ray analysis was done on a Syntex P_{21} diffractometer.

The following two experimental procedures exemplify the general method of synthesis of the compounds derived from *cis*- and *trans*-cyclohexane-1,2-dicarboxylic anhydrides.

Reaction of Methylhydrazine (1) with *cis*-Cyclohexane-1,2-dicarboxylic Anhydride (3). A mixture of 5.0 g (0.038 mol) of **3** and 1.75 g (0.038 mol) of **1** was left at room temperature for 24 h at which time the reaction was complete, determined by using TLC. The semisolid residue was washedseveral times with cold CCl_4 and dried to give 5.50 g (80%) of a mixture of **6** and **8** with a ratio of 70:30 (estimated from the NMR spectrum of the mixture). The imide **6** dissolved out of the mixture by using hot CCl_4. The sample of **6** for analysis was crystallized from a mixture of heptane and MeOH. The CCl_4-insoluble residue, **8**, was crystallized from a mixture of benzene and MeOH.

Reaction of 1,1-Dimethylhydrazine (2) with *trans*-Cyclohexane-1,2-dicarboxylic Anhydride (4). A mixture of 5.0 g (0.038 mol) of **4** and 5.40 g (0.09 mol) of **2** was heated under reflux for 12 h at which time the reaction was complete, determined by using TLC. The excess **2** was evaporated. The product was dried to give 7.50 g of a mixture of **13**, **19**, and **20** in the approximate ratio of 30:10:50, determined from the NMR spectrum. This mixture was heated in three successive 75-ml portions of CCl_4. The residue was filtered and dried to give 3.25 g (40%) of **20**. The combined filtrates were evaporated to dryness. This solid was heated in three successive 75-ml portions of heptane. The heptane-insoluble residue was dried to give 0.6 g (8%) of **19**. Evaporation of the combined filtrates, followed by washing and drying of the residue, afforded 2.25 g (30%) of **13**.

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Registry No.—**1**, 60-34-4; **2**, 57-14-7; **3**, 13149-00-3; **4**, 14166-21-3; **6**, 18886-75-4; **7**, 60498-47-7; **8**, 60498-48-8; **9**, 60498-49-9; **10**, 60498-50-2; **12**, 60498-52-4; **13**, 18886-73-2; **14**, 60498-53-5; **17a**, 60498-54-6; **17b**, 60498-55-7; **19**, 60387-17-9; **20**, 60498-56-8.

References and Notes

(1) For the previous paper in this series, see J. Nematollahi, S. Kasina, and D. Maness, *J. Heterocycl. Chem.*, **11**, 351 (1974).
(2) Support of this investigation by the University of Texas Research Institute is gratefully acknowledged.
(3) There are a number of currently employed chemotherapeutic compounds with hydrazine moieties and imide structures. Tuberculostatic isonicotinic acid hydrazide, anticonvulsant substituted succinimides, and antihypertensive 1-hydrazinophthalazine may be cited as examples. Additionally, we are planning to employ some of our bicyclic compounds for azasteroids synthesis.
(4) S. Simonsen, R. Loghry, J. Nematollahi, and S. Kasina, *J. Heterocycl. Chem.*, **13**, 936 (1976).
(5) S. Simonsen and J. Nematollahi, unpublished results.
(6) We have observed that a homogeneous mixture of 1,1-dimethylhydrazinium salt of a carboxylic acid and 1,1-dimethylhydrazine gives dimethylammonium salt (see also ref 1). The absence of such species in the reaction of **4** with **2** is due to the precipitation of the hydrazinium salt, **17b**, from the reaction mixture.

A Unique Rearrangement of 3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones to 3-Methylamino-4(3*H*)-quinazolinones[1]

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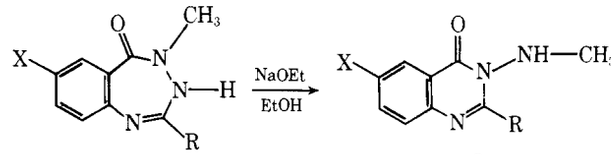
Ring contractions of benzo-fused seven-membered heterocyclics are well known in the literature and the field has recently been reviewed.[2] The majority of these rearrangements involve 1,4-benzodiazepines being converted to quinazolinones and quinoxalines but there are additional examples involving 1,5-benzodiazepines, various benzoxazepines, and benzothiazepines. However, with the exception of a photocatalyzed contraction of 3,1,4-benzoxadiazepines and an acid-induced rearrangement of 1,2,5-benzotriazepines, there have been very few studies on three heteroatom seven-membered systems.[3,4]

Recently we reported the synthesis of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**2a–g**) by the reaction of anthranilhydrazides[5] (**1**) and ortho esters.[6] We have found these benzotriazepines to be extremely labile to alkoxide-induced ring contraction to 3-methylamino-4(3*H*)-quinazolinones (**3a–g**) (Scheme I).

Scheme I



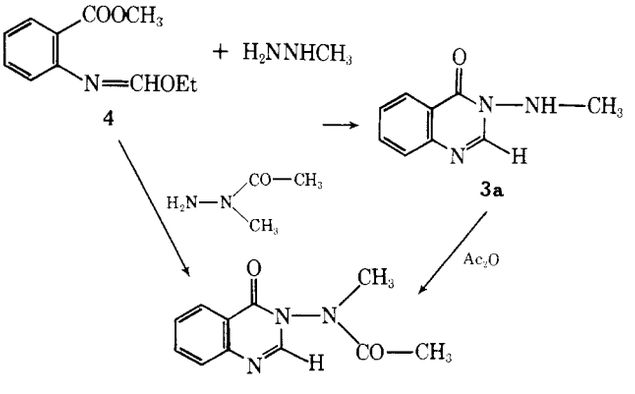
2 **3**

The latter products were identified by unique features of their ^1H NMR spectra, for example, an *N*-methyl doublet at δ 2.47–2.85 and a mutually coupled NH quartet at δ 6.17–6.38. Both of these resonances were considerably more shielded than the corresponding groups in the initial benzotriazepine, e.g., in **2a** the *N*-methyl appeared as a singlet at δ 3.22 and the NH as a doublet (coupled to C_2 H) at δ 8.65.

Upfield shifts for both the *N*-methyl and the NH resonances would be in accord with their rearrangement into loci no longer α to the deshielding influences of the nodal planes of the C=O and the N_1–C_2 double bond in **2a–g**. Furthermore, the presence of a newly formed $-NHCH_3$ moiety in the product is evidenced by the observed splittings.

Additional support for the assignment of the rearrangement products as 3-methylamino-4(3*H*)-quinazolinones was provided by alternative syntheses (Scheme II). Methyl 2-eth-

Scheme II



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